REMARKS

Applicants respectfully request entry and consideration of the present amendment under 37 C.F.R. § 1.116(a) because numerous rejected claims have been canceled, placing the application in condition for allowance or in better form for appeal. In addition, as discussed in more detail below, because the Examiner did not properly consider the Second Declaration submitted with the last reply, Applicants respectfully request that the Examiner withdraw the finality of the present office action, and enter and properly consider the Second Declaration and the arguments presented regarding the Second Declaration in this and in the previous response.

Claims 1-81, 83-86 and 98 are canceled without prejudice. Applicants reserve the right to purse the canceled subject matter in one or more continuing applications. Claims 87-96 have been amended merely to depend from a non-canceled claim. New claims 100 and 101 have been added merely to split the two recited fragments in claim 82 into separate dependent claims. No new matter has been added. Claims 82, 87-97 and 99-101 are pending and under examination.

A notice of appeal is being filed herewith.

The Declaration

The Office Action states:

> the Dr. Detmar's declaration filed on 5 September 2003 will not be considered in this Office action because it is not clear at this time whether the declaration was intended for the instant application or application with 09/536,087. The Office's record shows that the attorney docket number for the instant application is 10287-051002/MGH 1470.2 as it appears on the declaration. However, the serial number on the declaration does not match with the instant application number.

In the response filed on September 5, 2003, in the present application, Applicants noted **"As discussed in the enclosed Second Declaration of Michael Detmar under 37 C.F.R. § 1.132 (copy enclosed), originally filed in the parent application in an Amendment of July 30, 2003, one or ordinary skill in the field of angiogenesis would understand that inhibition of one of the steps of angiogenesis would inhibit growth of any angiogenesis-dependent tumor."** (See page 17, first paragraph) Thus, Applicants very clearly indicated that that the

Second Declaration was filed in the parent application, but a copy was being submitted in the present application as evidence in support of enablement of the claims in the present case. Applicants thus request that the finality of the present office action be withdrawn and that the Examiner properly consider the Declaration and the arguments regarding the Second Declaration in the present case.

Specification

The Examiner asked that Applicants confirm that the application entitled "Delivery of Thrombospondin from Implantable Tissue Matrices" (U.S.S.N. 09/822,161), which was cited in an IDS filed with the response on September 5, 2003, was a copy of the IDS filed on November 25, 2002. Applicants confirm that a copy of the reference mailed with the response on November 19, 2002 was provided in response to the Examiner's objection to the IDS in the previous office action. **The application was cited as a reference in an IDS. It is not a substitute specification for the present application.**

Rejections Under 35 U.S.C. § 112, first paragraph

Enablement

Claims 54-73, 75-79, and 81-98 are rejected as failing to comply with the enablement requirement. Claims 1-81, 83-86 and 98 are now canceled. Claim 99 is not included in this rejection. The Examiner states:

> the base claims 54, 81, and 82 require making a construct expressing a TSP-2 fragment capable of inhibiting endothelial migration, wherein said fragment comprises at least 10 contiguous amino acids either [sic] a procollagen domain of TSP-2 or a type I repeat of TSP-2 for the purpose stated in the preamble of the claims....The specification does not provide guidance how to make a fragment thereof capable of inhibiting endothelial cell migration, wherein said fragment comprises at least 10 contiguous amino acids of a procollagen domain of TSP-2 let alone how to use said fragment in a method of treating a tumor.

This rejection is traversed. In support of the rejection, the Examiner notes data in Figure 7 of the specification which indicates that certain fragments of TSP-2 derived from procollagen domains did not inhibit endothelial cell migration. The reasoning of this grounds for rejection is flawed. That some of these fragments did not inhibit endothelial cell migration does not mean that the claims are not enabled. Applicants are not arguing that every peptide derived from the procollagen domain of TSP-2 inhibits endothelial cell migration, or that every peptide derived from a procollagen domain of TSP-2 will be useful for treating subjects with angiogenesis-dependent tumors. Rather, Applicants are urging that those fragments of TSP-2 which include at least 10 amino acids of a procollagen domain or a type I repeat of TSP-2 and are capable of inhibiting endothelial cell migration (as recited in the claims) are enabled for the claimed methods. Methods of generating fragments of TSP-2 are exemplified, and are known in the art. Applicants have also disclosed and shown data for assays for determining if a fragment of TSP-2 inhibits endothelial cell migration. Thus, the assertion that "the specification does not provide guidance how to make a fragment thereof capable of inhibiting endothelial cell migration" is incorrect. **Applicants have shown that a recited fragment's ability to inhibit endothelial cell migration correlates with the ability to treat an angiogenesis-dependent tumor in vivo** (the Examiner is again urged to consider the previous arguments and declarations that have not yet been properly considered on this point). Therefore, the claims are enabled.

The question is not whether it is possible to make a fragment that does not work (as the Examiner seems to believe), but rather whether one of ordinary skill can produce, without undue experimentation, fragments that do work, in which the activity is not abolished. The demonstration that particular fragments did not inhibit endothelial cell migration in an assay merely indicates that the assay is useful for distinguishing functional from non-functional fragments, and therefore supports enablement.

The Examiner also implies that the claims are not enabled because they are not limited to use of the fragment described in the First Declaration. I.e., the Examiner states that "the argument shown at Fig. 3 of the specification and that data shown in the first Dr. Declaration [sic] is not commensurate in scope [sic] of the claims because the claims are not limited to a

construct expressing SEQ ID NO:2 or the specific fragment in the declaration." This is traversed. Applicants have described how to make and use multiple fragments of TSP-2 as recited in the claims. Ample guidance for making fragments of TSP-2 is provided by the specification, and other embodiments can be determined without undue experimentation. The ability of TSP-2 and the recited fragments to inhibit endothelial cell migration, as disclosed in the specification, correlates with the ability to treat an angiogenesis-dependent tumor in vivo (the Examiner is again urged to consider the previous arguments and declarations that have not yet been properly considered on this point). For example, Applicants have shown that TSP-2 fragments derived from the procollagen domain have biological activity. Applicants have also shown that the procollagen domain of TSP-2 inhibits tumor angiogenesis in vivo. See, e.g., Figure 3 of the Declaration filed with the response of November 19, 2002 ("the First Declaration"), which shows that growth of A431 tumors in mice injected with the procollagen domain (PC) was reduced relative to growth of tumors in mice injected with PBS. See also Figure 4 of the first Declaration, which also shows that tumors growing in mice injected with 1 mg/kg of the procollagen domain of TSP-2 had a smaller volume than tumors in control mice.

Furthermore, the Examiner acknowledged that the specification supports a fragment comprising an amino acid sequence encoded by nucleotides 294-1883 of SEQ ID NO:1. The fragment is similar to the fragment used in the Examples in the First Declaration, which corresponds to a polypeptide encoded by nucleotides 213-1883 of SEQ ID NO:1. In the Office Action mailed January 30, 2003, the Examiner issued a new matter rejection over claims directed to methods of using TSP-2 fragments comprising amino acid sequences encoded by nucleotides 294-1883 of SEQ ID NO:1. This rejection was argued in the reply sent on July 30, 2003 and was overcome (see page 21 of the reply mailed July 30, 2003). The genus of fragments recited in the claims includes a polypeptide encoded by nucleotides 213-1883 of SEQ ID NO:1. The fact that the specification does not contain *in vivo* data which uses a fragment identical to the fragment in the First Declaration does not render the claimed methods non-enabled. As discussed in previous responses, the law does not require Applicants to describe every conceivable

embodiment of the invention. Ample guidance is provided by the specification, and other embodiments can be determined without undue experimentation.

Moreover, the Examiner has not explained why she believes that guidance for use of the fragments has not been provided. As discussed in detail in the response filed on September 5, 2003, Applicants have demonstrated that tumor cells expressing TSP-2 implanted into an animal inhibit angiogenesis of the tumors. The specification describes assays in which tumor cells transfected with TSP-2 exhibited decreased angiogenesis in vivo as compared to control tumor cells (see, e.g., page 39, lines 22-25). Guidance for administering cells is provided, e.g., on pages 62 through 68 of the specification.

Finally, the Examiner notes several broad grounds for non-enablement where she states "considering unpredictability in the cancer treatment art, broad scope of claims, insufficient guidance with regard to various recited cancer treatments with various claimed products, it is maintained that undue experimentation would be required to practice the invention as claimed." The Examiner is respectfully requested to read and consider the detailed arguments in rebuttal of these grounds for non-enablement presented in the previous replies and 2 declarations filed in the present application. In summary, the claims have been substantially narrowed and recite specific structural and functional limitations of the recited fragments that are easily assayable. Applicants have shown that the claimed methods inhibit angiogenesis and tumor growth *in vivo* using art recognized models of angiogenesis-dependent tumors. The skill in the art is high and the guidance in the specification is substantial. Applicants have noted that the claimed methods are predictable for treatment of angiogenesis-dependent tumors because they inhibit at least one step of angiogenesis (i.e., endothelial cell migration), which correlates with tumor inhibition (see previous reply, where this is argued in detail). In view of the foregoing, Applicants request withdrawal of the rejection.

Rejections for New Matter

The Examiner rejected claims 54-73, 75-79, and 81-99 as containing new matter, stating that "although the specification...and the original claims have support for unwanted cell

proliferation, unwanted angiogenesis, benign or malignant unwanted cell proliferation, it does not have support for new limitation "an angiogenesis-dependent tumor."

This is traversed. There is ample support for this phrase in the specification as filed. See, e.g., page 2, lines 19-21 where it states that "the present invention is based, in part, on the discovery that overexpression of TSP-2 decreases tumor size in vivo. The invention features methods to modulate unwanted angiogenesis and tumor growth." Clearly, the treatment of tumors and inhibition of angiogenesis were contemplated at the time the specification was filed. The knowledge that tumors rely on angiogenesis was known at the time. See, for example, the first sentence of the Background, where it states that "in order to grow beyond minimal size and to metastasize, tumors need to induce the growth of new blood vessels (angiogenesis) providing a lifeline for tumor sustenance and waste disposal." (page 1, lines 10-12). Treatment of tumors is disclosed in the specification. Angiogenesis-dependence of tumors is also directly disclosed in the specification. As the Examiner is aware, whether particular technological information is new matter depends on the facts of the case, the nature of the disclosure, the state of the art, and the nature of the new matter. The disclosure and the state of the art amply support the phrase "angiogenesis-dependent tumors". Thus, treatment of angiogenesis-dependent tumors, while not disclosed *in haec verba*, does not constitute new matter. Applicants also note that the term "angiogenesis-dependent tumor" was suggested by Examiner Yu and Examiner Caputa in the interview of July 8, 2003 with the undersigned.

The Examiner also asserts that there is no support for "at least 10 contiguous amino acids of a procollagen domain." This rejection is respectfully traversed. The first full paragraph at page 23 explicitly discloses a fragment that is at least 10 contiguous amino acids of TSP-2. The embodiment where the fragment contains a type 1 repeat is only an embodiment, and not required for all fragments. The procollagen domain of TSP-2 is mentioned repeatedly throughout the application, and at page 44, at least 4 species of fragments containing at least 10 contiguous amino acids of the procollagen domain of TSP-2 are disclosed. Accordingly, the recitation of fragments containing at least 10 contiguous amino acids of a procollagen domain of TSP-2 are fragments does not constitute new matter.

In view of the foregoing, Applicants respectfully request that the rejection be withdrawn.

Enclosed is a Petition for Extension of Time along with the required fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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